## Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claims 2, 3, 6, 7, 20, 21, and 29 have been amended. Descriptive support for the amendments to claims 2 and 3 is found in the present application, as filed, at page 7, lines 20-22. Support for the amendments to claim 21 is found in the present application, as filed at page 13, lines 9-13. No new matter has been added. Claims 1-53 and 63-67 are pending, with claims 11, 31-53, and 63-67 being withdrawn from consideration.

There is considerable interest in the use, for a number of surgical or other therapeutic applications, of materials that adhere to biological tissues e.g., as an alternative to the use of mechanical fasteners such as sutures, staples, etc. Formulations of such materials that have hitherto been proposed include viscous solutions or gels that are either manufactured in that form or are prepared immediately prior to use by mixing of the ingredients. Such formulations are then applied to the tissue surface using a suitable applicator device such as a syringe.

Formulations of the type described above suffer from a number of disadvantages. If the formulation is of low viscosity, it may spread from the area of application and hence be difficult to apply precisely to the desired area of tissue. If the formulation is more viscous, on the other hand, it may be difficult to dispense. In either case, the formulation, being prepared in hydrated form, may have a limited lifetime and may be subject to premature curing. It may therefore be necessary for the whole of the formulation to be used at once or discarded. Also, the preparation of formulations immediately prior to use by mixing of ingredients is laborious and time-consuming. In addition to these drawbacks, the degree of adhesion between tissue surfaces that is provided by such formulations may be less than would be desired.

Formulations of tissue adhesive materials have also been applied to a suitable support for application to the tissue surface. The use of therapeutic materials in the form of a sheet, patch, or film, for topical administration to either internal or external organs of the body, is well documented for a wide range of medical applications. A disadvantage of products proposed hitherto, however, is that the degree of adhesion to the underlying tissue, particularly in the longer term, may be inadequate. While the initial adhesion may be satisfactory, the sheet may subsequently become detached from the tissue, often after only a few seconds or minutes, e.g., as a result of hydration of the sheet following its application. In

addition, the flexibility of the product may be insufficient for it to conform readily to the surface to which it is applied, which may also have an adverse effect on its adhesion.

As a result of the inadequate adhesion of these products, it may be necessary to provide further reinforcement, e.g., through mechanical attachment using sutures, staples, or the like. Alternatively, energy (e.g., light or heat energy) may be applied in order to initiate chemical bonding of the adhesive formulation to the underlying tissue, and hence bonding of the tissue surfaces to each other. Such approaches introduce further drawbacks. The use of mechanical fastening such as sutures or staples is often the very thing that the use of such products is intended to replace or avoid. In many instances, the use of such fastening is either not wholly effective (e.g., on the lung) or undesirable, as their introduction gives rise to further areas of tissue weakness. The use of external energy requires the provision and operation of a source of such energy. Such energy sources may be expensive and difficult to operate, particularly in the confines of an operating theatre or similar environment. Also, the use of external energy for attachment can be both time-consuming and (in some cases) requires significant careful judgment on the part of the surgeon to evaluate when sufficient energy has been delivered to effect attachment without damaging the underlying tissue.

The present invention is directed to improved formulations of tissue-adhesive materials and sheets or the like of the general type described above that overcome or substantially mitigate the above-mentioned and/or other disadvantages of the prior art.

The rejection of claims 8-10 and 12-22 under 35 U.S.C. § 112 (first para.) for lack of written description is respectfully traversed.

To begin, the position of the U.S. Patent and Trademark Office ("PTO") is somewhat unclear, because much of what is written at pages 3-4 of the office action appears to be irrelevant to the claimed invention. For example, in the last paragraph at page 3, the PTO directs its comments specifically to the term "inhibitor," yet this term does not appear in the rejected claims. Further, at page 4, the office action addresses compounds that inhibit downstream products of 14 kD PLA2. Again, no such subject matter is claimed in the present application. From the portion of the office action that does appear to pertain to the claimed invention (i.e., the middle paragraph at page 3), the PTO's position is that the present application lacks chemical structural information for what materials are encompassed by the phrase "wherein the material comprising tissue-reactive functional groups is formed by derivatization of a polymer precursor." Applicants respectfully disagree.

First, with respect to claims 20-22, these claims are dependent upon claim 1 and not rejected claim 8. Therefore, this rejection is at least improper with respect to these claims.

Regarding claims 8-10 and 12-19, the present application teaches at page 11, line 21 to page 12, line 26, that tissue-reactive material may be formed by derivatisation of a suitable polymer precursor. Classes of polymer which lend themselves to such derivatisation include those that contain carboxylic acid or alcohol functional groups, or related structures. Polymers that may be used include polymers that are commercially available or polymers that are prepared specifically for this purpose. Naturally-occurring materials such as sucrose or a derivatised cellulose may also be used.

Commercially available polymers that may be used include polyvinylalcohol ("PVA"). In the case of PVA, the functional groups may be introduced by first adding a chain extending or linking group, for example an acid functionality that can be further reacted with N-hydroxy succinimide. Figure 2 shows the addition of a chain-extending group to a copolymer of vinyl acetate and vinyl alcohol, the chain-extending group terminating in a carboxylic acid group that may be converted to the corresponding NHS-ester. The copolymer starting material (in which molar fraction $x$ of vinyl alcohol groups may be 0.85-0.995) is reacted with a cyclic anhydride (in the example illustrated, succinic anhydride) in the presence of a base such as pyridine. Between 5% and 40% of the alcohol groups are derivatised to form the carboxylic acid-bearing side chains (i.e., $a+b=x$, with $a$ being between $0.05x$ and $0.40x$), which may then be converted to the NHS-ester by conventional methods that are known *per se*.

Where the polymer support is synthesized for the purpose of subsequent derivatization, a wide variety of monomers may be used. Examples include *N*-vinyl-2-pyrrolidone, acrylic acid, vinyl acetate, vinyl acetic acid, mono-2-(methacryloyloxy)ethyl succinate, methacrylic acid, 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, (polyethylene glycol) methacrylate or other monomers containing acid or alcohol functionality. Such monomers may be polymerized via various standard polymerization techniques, including free radical techniques using an initiator such as benzoyl peroxide, 2,2'-azobisisobutyronitrile ("AIBN"), lauroyl peroxide, peracetic acid, etc. One preferred example of such a polymer is poly(N-vinyl-2-pyrrolidone-co-acrylic acid) polymerized using AIBN as initiator. The polymerization of this material is illustrated in Figure 3, in which the molar ratio of acrylic acid-derived units may be between 0 and 1.0, preferably less than 0.60,

and more preferably less than 0.40, e.g., between 0.025 and 0.25. The copolymer may be further reacted with N-hydroxysuccinimide to form the tissue-reactive material.

Additional descriptions of material comprising tissue-reactive functional groups formed by derivitization of a polymer precursor are provided in the present application at pages 12-17. Also, specific embodiments of these materials are described in the Examples of the present application.

The present application also teaches at page 10, line 30 to page 11, line 19, that tissue-reactive functional groups that may be of utility in the present invention are any functional groups capable of reaction (under the conditions prevalent when the formulation is applied to tissue, i.e., in an aqueous environment and without the application of significant amounts of heat or other external energy) with functional groups present at the surface of the tissue. The latter class of functional group includes thiol and amine groups, and tissue-reactive functional groups therefore include groups reactive to thiol and/or amine groups. Examples include imido ester, p-nitrophenyl carbonate, N-hydroxysuccinimide (NHS) ester, epoxide, isocyanate, acrylate, vinyl sulfone, orthopyridyl-disulfide, maleimide, aldehyde, and iodoacetamide. N-hydroxysuccinimide (NHS) ester is a particularly preferred tissue-reactive functional group.

In view of the foregoing, it is submitted that a person of ordinary skill in the art would have recognized that the inventors of the present application had possession of the claimed invention at the time the application was filed. Therefore, the rejection of claims 8-10 and 12-22 for lack of written description is improper and should be withdrawn.

The rejection of claims 2, 3, 6, 7, 21, and 29 under 35 U.S.C. § 112 (second para.) for indefiniteness is respectfully traversed in view of the above amendments.

The rejection of claims 1-10, 12-16, 19-20, and 28-29 under 35 U.S.C. § 102(b) as anticipated by German Patent Application No. DE 35 02 998 to Schönwald et al. ("Schönwald") is respectfully traversed.

In making this rejection, the PTO contends that the machine translation of Schönwald accompanying the office action teaches a tissue-adhesive formulation comprising a naturally occurring or synthetic polymerisable and/or cross-linkable material in particulate form and in admixture with particulate material comprising tissue-reactive functional groups, as required by claim 1 of the present application. The PTO refers to the following sections of Schönwald.

> On these ferromagnetic particles physiologically compatible plastics become applied, which, reactive groups coupling with

antibodies to exhibit. Appropriate ones are thus monomer solutions, those at least 2 Vinylkomponenten and a solvent contained. One of the monomers is over < RTI ID=5.1> kupplungsfähige< /RTI> Pendant groups order, as for example acrylic acid, Hydroxyethylacrylat, vinyl alcohol, acrylamide or other vinyl monomers, which have clutchable pendant groups. As comonomers such components become selected, to which such functional groups are missing, which are more copolymerizable however easy and lead to physiologically compatible plastics. Typical examples for this are 1-vinyl-pyrrolidone, vinyl acetate etc.

* * *

Examples for this are clutches over activated esters by means of Hydroxybenzotriazol and N-Hydroxysuccinimid.

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Example 1 ferromagnetic particle with a particle size between 0,5 and 1 at from the group that iron/rare earth alloys in the ratio 17:2 such as Fel7Pr2 and < RTI ID=7.1> Fel7Er2< /RTI> < RTI ID=7.2> and/or. Ferrites such as Co0,4Zn0,6Fe2O4 and Ni0,2Zn0,8Fe2 O4< /RTI> with Curie points between 42 and 500 C on the subsequent manner with a plastic layer are covered: Acrylic acid and 1-vinyl-pyrrolidone are copolymerisiert by additive by Azodiisobutyronitril. The particles become subsequent washed with hot water. The free carboxyl groups are < with; RTI ID=7.3> L-Hydroxybenzotriazol< /RTI> or N-Hydroxysuccinimid converted. The so obtained particles are able to form with amino group of proteins, in particular also antibodies and effect factors, Peptidbindungen. After the conversion with such antibodies or effect factors the particles become washed and in 5% - iger Dextroselösung suspends. These suspensions can be injected intravenous.

Nowhere in these passages (or anywhere else) does Schönwald teach or suggest a tissue-adhesive formulation comprising a naturally occurring or synthetic polymerisable and/or cross-linkable material in particulate form and in admixture with particulate material comprising tissue-reactive functional groups, as required by claim 1 of the present application. While Schönwald refers to "ferromagnetic particles," there is no indication in this reference that the "ferromagnetic particles" constitute a "polymerisable and/or cross-linkable material." Nor is there any indication in this reference of any other *particulate material* (i.e., a particulate material comprising tissue-reactive functional groups) in admixture with the ferromagnetic particles. Accordingly, Schönwald cannot be said to

teach or suggest each and every limitation of the claims. Therefore, the anticipation rejection based on this reference is improper and should be withdrawn.

The rejection of claims 1-4, 6-10, and 29-30 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 6,989,192 to Husemann et al. ("Husemann") is respectfully traversed.

Husemann is directed to pressure sensitively adhesive polyacrylate compositions to which there have been added crosslinked and functionalized polymer particles suitable for assisting a crosslinking reaction of the polyacrylates and thus for serving to prepare pressure sensitive adhesives. The pressure sensitively adhesive polyacrylates are obtained by free radical polymerization of a monomer mixture comprising (a) acrylic acid and methacrylic acid derivatives and (b) vinyl, acrylic, and/or methacrylate monomers containing a group X capable of chemical coupling. The polymer particles are said to contain at least two functional groups, Y and Z, which are capable of chemical coupling with the functional group X in the form of a substitution or addition reaction.

However, Husemann does not teach or suggest a naturally occurring or synthetic polymerisable and/or cross-linkable material *in particulate form and in admixture with particulate material* comprising tissue-reactive functional groups as required by claim 1. In the outstanding office action, the PTO has taken the position that Husemann teaches cross-linkable polyacrylate particles in admixture with particles comprising a functional complex. However, as described in column 5, lines 18-50 of Husemann, crosslinked pressure sensitive adhesives are prepared by (i) preparing the polyacrylate by free radical polymerization of a monomer mixture, (ii) concentrating the pressure sensitive adhesive to a *melt* having a solvent content, and (iii) blending the pressure sensitive adhesive in the *melt* with crosslinked and functionalized polymer particles below a critical reaction temperature. A crosslinking reaction is then carried out by bringing the temperature of the adhesive to at least the critical reaction temperature T so that the coupling reaction between the functional group X of the polyacrylate and the functional groups Y and Z of the polymer particles is obtained. Husemann further states at col. 6, lines 60-61, that the mixing of the functionalized polymer particles takes place as a function of the viscosity of the acrylic *hotmelt*. The polyacrylate is applied preferentially from the *melt* as a *film* on a backing or on a backing material (Husemann, col. 7, lines 65-67). In other words, Husemann teaches blending a pressure sensitive adhesive *melt* with polymer particles, and not an admixture of a polymerisable and/or cross-linkable material in particulate form with particulate material comprising tissue-reactive functional groups, as required by the present claims.

Husemann also does not teach or suggest an admixture containing *particulate material comprising tissue-reactive functional groups*, as required by claim 1 of the present application. At page 8 of the office action, the PTO asserts that Husemann's functional group X can be aldehyde, which is a tissue-reactive functional group. However, as described above, functional group X is contained in the pressure sensitively adhesive polyacrylates and not the polymer particles. Since the pressure sensitively adhesive polyacrylates of Husemann are described as a melt and/or film (but not particulate material), Husemann cannot be said to teach or suggest a particulate material comprising tissue-reactive functional groups as required by the present claims, let alone these materials in an admixture with polymerisable and/or cross-linkable material in particulate form. Further, since the polymer particles are crosslinked to the polyacrylate during manufacture, functional group X is no longer available in the manufactured product for crosslinking to tissue.

Since Husemann does not teach or suggest each and every aspect of claim 1 (and claims 2-4, 6-10, and 29-30 dependent thereon), the obviousness rejection based on this reference is improper and should be withdrawn.

The rejection of claims 17-18 and 21 under 35 U.S.C. § 103(a) for obviousness over Schönwald in view of PCT Publication No. WO 03/094898 to Childs et al. ("Childs") is respectfully traversed.

Childs is cited for teaching biomedical applications of N-vinylpyrrolidone and optimum molar ratios of ionically cross-linkable polymeric material to ethylenically unsaturated molecules. However, Childs does not overcome the above-noted limitations of Schönwald. Therefore, the obviousness rejection of claims 17-18 and 21 is improper and should be withdrawn.

The rejection of claims 22 and 30 under 35 U.S.C. § 103(a) for obviousness over Schönwald is respectfully traversed.

According to the PTO, it would have been obvious to one of ordinary skill in the art at the time of the invention to optimize the formulation of the claimed invention as set forth in claims 22 and 30. This rejection is based on the PTO's position that Schönwald teaches or suggests all of the limitations of claim 1 (from which claims 22 and 30 depend). However, as noted above, Schönwald fails to teach or suggest all of the limitations of claim 1 and, therefore, cannot be said to render dependent claims 22 and 30 obvious. Therefore, this rejection is improper and should be withdrawn.

In view of all of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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